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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/446,317	Applicant(s) Wagner et al
	Examiner Richard Schnizer	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 19, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *35-38, 40, 41, 43-52, and 54-68* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *35-38, 40, 41, 43-52, and 54-68* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☒ The proposed drawing correction filed on *Jul 31, 2000* is: a) ☒ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/19/03 has been entered.

The Declaration of Dr. Plank was received an entered as paper No. 27 on 3/19/03.

An amendment was received and entered as Paper No. 26 on 3/19/03. Claims 39 and 42 were canceled as requested.

Claims 35-38, 40, 41, 43-52 and 54-68 remain pending and are under consideration in this Office Action.

Rejections Withdrawn

The rejections of claims 35-38, 40, 41, 43-52 and 54-68 under 35 USC 112, first paragraph, are withdrawn in view of Applicant's amendments and arguments, and the Declaration of Dr. Plank.

After further consideration, and in view of the Declaration of Dr. Plank, the objection to the specification for the introduction of new matter over the term "random branched" is withdrawn.

The rejections of record under 35 USC 103 are withdrawn in favor of the following new grounds of rejection.

Claim Objections

Claims 58-64 are objected to because they are ungrammatical. These claims should begin with an article. It is suggested that claims 58 and 64 should begin with "A", and claims 59-63 should begin with "The".

Claim 46 is objected to because the words "polymer" and primary' are joined by a colon. Deletion of the colon and separation of these words by a space is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-38, 40, 41, 43-52, and 54-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36-38, 40, 41, 43-52, and 54-57 are indefinite because it is unclear to which of the

complexes of claim 35 these claims are drawn. These claims do not begin with a definite article, so it is unclear to which of the complexes embraced by claim 35 these claims refer.

Claim 58 is indefinite because it is unclear as to whether DNA may be modified with a cellular ligand, or whether only PEI may be modified with a cellular ligand.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35-38, 40, 41, 43-48, 58-60, aud 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plank et al (Human Gene Therapy (1996) 7: 1437-1446).

Plank renders obvious a species of the claimed invention. Plank teaches that the stability of polycation/DNA complexes in blood can be enhanced by covalent modification of the polycation with polyethyleneglycol (PEG), thereby reducing complement activation after intravenous administration. See abstract and overview summary. Plank exemplifies covalent modification of polylysine/DNA complexes at a 2:1 charge ratio with a l- to 10-fold excess of PEG over the reactive amino groups. See page 1440, first full paragraph; and page 1445, column 1, lines 1-7 of first full paragraph. The molecular weight of PEG ranged from 1000-12000. See

page 1445, lines 1-3. This covalent addition of PEG resulted in reduced complement activation by the synthetic polycation/DNA complexes. Plank also shows that complexes of PEI 25000 (Aldrich) with DNA (2:1 mass ratio) stimulate complement activation.

Plank does not exemplify complexes comprising PEI covalently attached to a hydrophilic polymer, and does not teach the charge ratios set forth in claims 36-38, or the compositions comprising hydrophilic polymer-modified polycation/DNA complexes in the concentration range of 0.2 mg/ml to 1 mg/ml required by claims 63, 64, and 66.

It would have been obvious to one of ordinary skill in the art at the time of the invention to covalently modify PEI/DNA complexes with PEG. One would have been motivated to do so for the following reasons. (1) Plank teaches that complement activation is a potential limiting factor for gene delivery of synthetic DNA complexes, and that appropriate formulation of DNA complexes can minimize or avoid this problem. See page 1437, column 2, lines 7-12. (2) Plank teaches that masking the surface of cationic DNA complexes with a covalently attached steric stabilizer such as PEG may be essential for intravenous delivery. (3) Plank teaches that PEI is a commonly used gene transfer vehicle, and that PEI/DNA complexes stimulate complement activation. See page 1438, paragraph bridging columns 1 and 2; and page 1441, column 2, lines 1-9. And (4), Plank shows that complement activation of PLL/DNA complexes is reduced by PEG modification. Thus one of ordinary skill in the art, given the totality of the teachings of the prior art, clearly would be motivated to covalently modify the surface of PEI/DNA complexes

with a steric stabilizer such as PEG, and would do so with a reasonable expectation that this would reduce complement activation by the complex, and prolong its half-life in circulation.

Regarding the charge ratios set forth in claims 36-38, it is clear that charge ratio is a result-effective variable that is routine to optimize. See Fig. 4 at page 1442 which shows that a greater PEI to DNA ratio results in lower complement activation. Generally, differences in concentration. will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that this concentration is critical. See MPEP 2144.05(b). In this case Plank teaches, in the context of PLL/DNA complexes, charge ratios in the range of claims 36 and 37, and fails only to teach the narrower range of charge ratios of claim 38. Because the ratio range of claim 38 is narrower than the other claimed ranges, it is clear that this rage is not critical for function of the invention and may be arrived at by optimization. One of ordinary skill in the art, given the teachings of Plank, would be motivated to use the charge ratios exemplified therein as a starting point for optimization. Similarly, the concentrations of DNA in claims 59-60 are routinely optimized because the concentration of DNA affects the charge ratio.

Finally, the concentrations of complexes in claims 63, 64, and 66 are not disclosed as critical, and it would be routine to optimize this parameter because one would reasonably expect the amount of gene expression observed to vary with the amount of complexes delivered, and increasing the DNA/polycation:PEG complexes of Plank would allow one to deliver more complex per administration.

It is noted that the specification teaches that PEI 25000, from Aldrich, is random branched.

Thus the invention as a whole was prima facie obvious.

Claims 35-38, 40, 41, 43-48, 58-60, and 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plank et al (Human Gene Therapy (1996) 7: 1437-1446) in view of either one of Zalipsky et al (US Patent 5,631,018, issued 5/20/1997) or Unger (US Patent 5,705,187, issued 1/6/1998).

The teachings of Plank are described above. Plank renders obvious synthetic DNA complexes wherein the complex is covalently modified with a hydrophilic steric stabilizer such as PEG. See page 1445, last sentence. More specifically, Plank renders obvious complexes of PEI and DNA wherein the PEI is covalently modified with PEG.

Plank does not explicitly teach the use of polyvinylpyrollidones, polyacrylamides, polyvinylalcohols, or copolymers of these, as hydrophilic steric stabilizers.

Zalipsky teaches that PEG may be used to increase the stability of liposomes in the bloodstream. See column, 2, lines 10-12. Zalipsky also teaches that polyinylpyrrolidone (PVP) or polyacrylamides including polymethacrylamide and polydimethylacrylamide may be substituted for PEG, or copolymerized with it. See column 2, lines 20-30, and lines 36-47.

Unger teaches that liposomes can be stabilized for delivery into the blood by covalent attachment of PEG, PVP, or polyvinylalcohol (PVA). See abstract and column 18, lines 3-13.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute PVP, PVA, polyacrylamides, or copolymers thereof, for the PEG of Plank. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Also, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). It is apparent from the teachings of Zalipsky and Unger that PVA, PVP, polyacrylamide, or copolymers thereof were recognized in the art as equivalent to PEG inasmuch as they could be used to stabilize liposomes in the bloodstream. Plank showed that PEG modification of polylysine DNA complexes results in a reduced propensity to activate complement, and should therefore stabilize these complexes in the bloodstream. Plank also suggested that other hydrophilic polymers could be used to stabilize other cationic DNA complexes. Thus one would have been motivated to use any of PEG, PVA, PVP, polyacrylamide, or copolymers thereof to stabilize PEI/DNA complexes, and the invention as a whole was prima facie obvious.

Claims 35, 49-51, 54, 55, 65, 67, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plank (1997), Zalipsky (1997) and Unger (1998), as applied to claims 35-38,

40, 41, 43-48, 58-60, and 63-65 above, and further in view of Curiel et al (US Patent 6,077,663).

The teachings of Plank (1997), Zalipsky (1997) and Unger (1998) are described above.

These references do not teach PEI modified with a cellular ligand, a nucleic acid that encodes a cytokine, or a tumor antigen.

Curiel teaches compositions comprising polycations complexed with nucleic acids, wherein the polycation is conjugated to an internalizing factor. See abstract; column 25, lines 20-26; column 29, lines 17-24 and claim l, column 91. The polycation may be PEI. See column 25, lines 20-26. The internalizing factor may be transferrin or EGF. See column 24, lines 7, 8, and 26. Curiel teaches that conjugation may be by covalent means. See column 34, line 28 to column 35, line 21. The nucleic acid may encode a cytokine or a tumor antigen. See e.g. column 25, lines 59-64; and column 33, lines 32-36.

It would have been obvious to one of ordinary skill in the art at the time of the invention to attach a targeting ligand of Curiel, such as transferrin or EGF, to the PEI of Plank because this allows receptor mediated endocytosis, and Curiel teaches that receptor-mediated endocytosis has major advantages for DNA delivery such as a non-toxic mechanism of passage through the cell membrane. See column 4, lines 52-55. It would also have been obvious to use a nucleic acid encoding a cytokine or a tumor antigen because Curiel teaches that such nucleic acids should be delivered to cells. See e.g. column 25, lines 59-64; and column 33, lines 32-36.

Claims 35, 49, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Plank (1997) in view of Zalipsky (1997), Unger (1998), Curiel (US Patent 6,077,663) and Blume et al (Biochim. Biophys. Acta (1993) 1149:180-184).

The teachings of Plank (1997), Zalipsky (1997), Unger (1998), and Curiel are described above and can be combined to render obvious a composition comprising a complex of random branched PEI and DNA, wherein the PEI is covalently modified with a hydrophilic polymer such as PEG and a targeting ligand. Plank teaches that addition of hydrophilic polymers, such as PEI, to DNA delivery compositions should increase their stability after intravenous injection.

These references in combination do not teach that the targeting ligand should be attached to PEI via the hydrophilic polymer.

Blume teaches PEG-modified cationic liposomes in which a targeting ligand is attached to the liposomes via the PEG polymer. Blume teaches that targeting ligands attached to the lipid-bilayer surface of PEG-modified liposomes had little or no capability of binding their targets. In contrast, attachment of targeting ligands to the distal end of the PEG coating resulted in ligand-directed binding. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to further modify the invention of Plank, as modified by Zalipsky, Unger, and Curiel, by attaching a targeting ligand to the distal end of the hydrophilic polymer molecules. One would have been motivated to do so in order to increase the availability of the targeting ligand to its cognate receptor, and in view of the teachings of Blume, would have had a reasonable expectation of success.

Claims 35, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plank (1997), Zalipsky (l. 997) and Unger (1998) as applied to claims 35-38, 40, 41, 43-48, 58-60, and 63-65 above, and further in view of Ezzidine et al (New Biol. (1991) 3(6): 608-614).

Plank (1997), Zalipsky (1997) and Unger (1998) can be combined to render obvious a composition comprising a nucleic acid and random branched PEI, wherein the random branched PEI is covalently bound to a hydrophilic polymer.

These references do not teach a nucleic acid encoding a suicide gene.

Ezzidine teaches a method of transfecting cells in vivo using retroviral vectors comprising a nucleic acid encoding herpes simplex thymidine kinase. See abstract.

It would have been obvious to one of ordinary skill in the art to substitute the PEI/DNA transfection complexes of Plank, Zalipsky, and Unger for the retroviruses of Ezzidine. One would have been motivated to do so in order to avoid the possibility of insertional mutagenesis inherent in the use of retroviruses. This would also allow the inclusion of other genes such as those encoding detectable markers, whereas retroviruses would be less advantageous for this purpose in view of restrictions on the amount of genetic material one can incorporate.

Thus the invention as a whole was prima facie obvious.

Claims 35, 58, 59, 61, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plank (1997), Zalipsky (1997) and Unger (1998) as applied to claims 35-38, 40, 41, 43-48, 58-60, and 63-65 above, and further in view of Boussiff et al (PNAS (1995) 92: 7297-7301).

The teachings of Plank (1997), Zalipsky (1997) and Unger (1998) are described above.

These references render obvious a process of complex formation in a salt concentration that is equal to, but not less than, that of HBS. See e.g. page 1439, column 2, lines 8-12 aud page 1440, column 1, first full paragraph. The combined references do not teach the use of deionized water as required by instant claims 61 and 62.

Boussiff teaches that DNA condensation by PEI is affected by the nature and concentration of all ions present in the solution..

It would have been obvious to one of ordinary skill in the art at the time of the invention to perform complex formation in a buffer containing a lower salt concentration than that found in HBS, and to do so in deionized water. One would have been motivated to vary the concentration of salt because Boussiff teaches that ion concentration is a variable that affects the results of DNA condensation by PEI. As discussed above, differences in concentration generally will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that this concentration is critical. See MPEP 2144.05(b). There is no evidence that it is critical to use salt at a concentration less than that in HBS. It is standard laboratory practice to use deionized water, and one would have been further motivated to do so in this case in order to control more carefully the amount of ions present in the complexing process.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 3/20/03 have been fully considered, but they do not apply to the new grounds of rejection set forth above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.